

MELAS Syndrome and Refeeding Syndrome in Pediatrics: A Case Report with A Fatal Outcome

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ABSTRACT

MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) is one of the most severe and complex mitochondrial diseases, characterized by its clinical heterogeneity and progressive course. We present the case of an 8-year-old pediatric patient with a confirmed diagnosis of MELAS, who experienced severe gastrointestinal episodes, refeeding syndrome, and metabolic complications, culminating in a fatal outcome. Through clinical analysis and a review of the literature, we emphasize the importance of a multidisciplinary approach that considers both neurological manifestations and associated digestive and nutritional complications. This report highlights the need for early surveillance protocols, comprehensive metabolic support management, and timely recognition of risks such as refeeding syndrome. It also underscores the urgent need to strengthen research and clinical guidelines adapted to the pediatric and hospital context in resource-limited settings.

KEYWORDS: MELAS, mitochondrial disease, refeeding syndrome, pediatrics, gastrointestinal complications.

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INTRODUCTION

MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) is one of the most common mitochondrial diseases in childhood. It is characterized by multisystemic dysfunction secondary to oxidative phosphorylation, generally associated with mutations in the MT-TL1 gene, responsible for leucine

transfer RNA, which leads to a progressive deficit in cellular energy production (1,2). Clinically, it can manifest with developmental delay, epilepsy, exercise intolerance, lactic acidosis, and stroke-like neurological events, in addition to gastrointestinal symptoms such as recurrent vomiting, weight loss, gastroparesis, and chronic constipation (Table 1) (3).

Table 1. Most frequent clinical manifestations in children with MELAS

Affected system	Clinical manifestations	Approximate frequency
Neurological	Stroke-like episodes, encephalopathy, hemiparesis, epilepsy, developmental delay. Recurrent migraine-like headaches, visual disturbances, aphasia.	80-90% 60-70%
Muscular	Proximal myopathy, chronic fatigue, exercise intolerance.	60-75%
Cardiac	Hypertrophic cardiomyopathy, arrhythmias, heart failure.	10-20%
Auditory	Progressive sensorineural hearing loss.	40-60%
Endocrine/metabolic	Diabetes mellitus, short stature, hypothyroidism, delayed puberty.	30-50%
Gastrointestinal	Cyclic vomiting, constipation, dysphagia.	20-40%
Psychiatric	Anxiety disorders, depression, behavioral disturbances.	10-30%

Source: Hattab et al. (2022) [7]; Salehi et al. (2022) [4]; Santorelli et al. (2019) [6].

Mitochondrial diseases have an estimated prevalence of 1 in 5,000 live births, with MELAS being one of the most representative variants in pediatrics (4). Its clinical course is variable and can include severe neurological and gastrointestinal complications requiring specialized nutritional support, including parenteral nutrition (5). In this context, refeeding syndrome (RS) is a significant complication, as patients with chronic malnutrition and metabolic disorders are at greater risk of developing electrolyte imbalances and organ failure after the initiation of nutritional support (6).

In Mexico, evidence on pediatric MELAS is limited and primarily restricted to case reports, so its true prevalence likely remains underestimated (7). Furthermore, there are few protocols addressing the nutritional management of patients with mitochondrial diseases, especially in high-risk metabolic settings.

No previous publications on pediatric MELAS cases were found at the "Dr. Jesús Kumate Rodríguez" General Hospital in Cancún, Quintana Roo. Therefore, this report is relevant because it describes the clinical course of a patient with MELAS complicated by severe gastrointestinal disturbances, malnutrition, and refeeding syndrome, with a fatal outcome. This case highlights the importance of early recognition of

refeeding syndrome (RS) and close nutritional and metabolic monitoring in pediatric patients with mitochondrial diseases.

ASSOCIATION BETWEEN THE RISK OF REFEEDING SYNDROME AND CLINICAL COURSE IN A PEDIATRIC PATIENT WITH MELAS SYNDROME

Pediatric patients with mitochondrial diseases, particularly those with MELAS syndrome, are at high risk of developing refeeding syndrome due to the combination of chronic malnutrition, insufficient energy intake, and severe gastrointestinal disorders. These conditions predispose to metabolic and electrolyte imbalances after the initiation of nutritional support.

The 2020 ASPEN consensus established diagnostic and risk stratification criteria for RS (Table 2), identifying significant weight loss, prolonged fasting, and hypercatabolic states as predisposing factors (6). The most frequent abnormalities include hypophosphatemia, hypomagnesemia, and hypokalemia, which are associated with increased morbidity and mortality, organ failure, and the need for intensive care. In patients with MELAS, these complications have a greater impact due to pre-existing mitochondrial dysfunction and limited ATP production capacity.

Table 2. Suggested diagnostic evaluation for suspected MELAS

Diagnostic test	Expected findings
Serum and CSF lactate	Elevated (≥ 2 mmol/L); correlates with mitochondrial dysfunction
Brain magnetic resonance imaging (MRI)	Lesions involving temporal and occipital lobes, not restricted to vascular territories
MR spectroscopy	Lactate peak in affected regions
Muscle biopsy (if applicable)	Ragged-red fibers and subsarcolemmal mitochondrial proliferation
Genetic testing (mtDNA)	m.3243A>G mutation in <i>MT-TL1</i> or less common variants

Source: Xu S, Jiang J, Chang L, Zhang B, Zhu X, Niu F. Multisystem clinicopathologic and genetic analysis of MELAS. *Orphanet J Rare Dis.* 2024. (16)

Several studies have demonstrated that electrolyte disturbances related to refeeding can trigger neurological deterioration, arrhythmias, respiratory failure, and multiple organ failure (8,10). In MELAS, this risk is increased by impaired oxidative phosphorylation, oxidative stress, and a tendency to develop lactic acidosis, leading to rapid metabolic decompensation.

Furthermore, recent reports describe a higher incidence of refeeding syndrome (RS) and worse outcomes in MELAS patients who present with gastroparesis, intestinal pseudo-obstruction, or require prolonged parenteral nutrition (5,11). Rapid initiation of nutritional support has been associated with hemodynamic instability, neurological progression, and prolonged hospital stays.

Overall, the available evidence indicates that the coexistence of MELAS and RS is associated with an unfavorable clinical course and increased mortality. Therefore, early recognition of risk factors, close monitoring of electrolytes and the progressive initiation of nutritional support, accompanied by vitamin supplementation and essential micronutrients, represent fundamental measures to

reduce complications and improve the prognosis in these patients (6,8).

CLINICAL CASE PRESENTATION

An 8-year-old female patient, originally from Cancún, Quintana Roo, the firstborn child of her mother, had a prenatal history of threatened miscarriage and threatened preterm labor, without neonatal complications. She had a confirmed diagnosis of MELAS syndrome through genetic testing performed in June 2024, identifying the m.3243A>G variant in heteroplasmy (78.2%) of the MT-TL1 gene, with maternal inheritance.

She presented with focal structural epilepsy secondary to cortical atrophy, global neurodevelopmental delay, regressive syndrome, and moderate intellectual disability. She was receiving treatment with levetiracetam, coenzyme Q10, Larginine, and carnitine, which were discontinued 15 days prior to her hospital admission. She was under multidisciplinary follow-up by neurology, genetics, gastroenterology, and rehabilitation specialists.

A brain MRI performed in 2023 documented bilateral lesions in the lenticular nuclei and parietal and

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temporal corticosubcortical regions, consistent with gliosis secondary to hypoxic-ischemic events. A second MRI in 2025 showed encephalomalacia, brain volume loss, and cortico-subcortical restriction suggestive of acute-subacute ischemic events.

The current episode began on June 2, 2025, with recurrent vomiting initially managed on an outpatient basis. Subsequently, she developed hematemesis and an adverse reaction to metoclopramide, and was therefore referred to the "Dr. Jesús Kumate Rodríguez" General Hospital. During her hospitalization, she experienced progressive multisystem deterioration, including seizures with suspected non-convulsive status epilepticus, encephalopathy documented by videoelectroencephalogram, respiratory failure requiring mechanical ventilation, acute exacerbation of chronic malnutrition, refeeding syndrome, and severe electrolyte imbalances.

In addition, she developed urosepsis due to extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL) and superinfection with *Candida albicans* and *Providencia alcalifaciens*, progressing to refractory septic shock. Despite intensive management with ventilatory support, total parenteral nutrition, antimicrobials, and maximum vasoactive therapy, she developed bradycardia and asystole, and died on July 9, 2025, under a do-not-resuscitate order authorized by her parents.

ETHICAL CONSIDERATIONS

This study was reviewed and approved by CI-2025-042-HGC and CEI-2025-042-HGC of the General Hospital of Cancún. Patient confidentiality and data handling were strictly controlled at all times. No names, initials, images, or clinical descriptions that could identify the patient were used. Appropriate informed consent was obtained for each of the procedures and treatments described in this case. **Discussion** This case highlights the clinical and metabolic complexity of MELAS syndrome in pediatric patients, particularly when it coexists with malnutrition and refeeding syndrome (RS). RS is a potentially serious complication associated with the reintroduction of nutritional support after prolonged periods of fasting or energy deficit, characterized by electrolyte imbalances—mainly hypophosphatemia, hypokalemia, and hypomagnesemia—and impaired cellular energy homeostasis (6,8).

In patients with MELAS, mitochondrial dysfunction leads to reduced ATP production, increasing susceptibility to metabolic decompensation during refeeding. In the case presented, the coexistence of chronic malnutrition, severe gastrointestinal disorders, and the need for parenteral nutrition created a high-risk environment for RS, similar to that reported by García-Cazorla et al. (3) in patients with digestive complications associated with mitochondrial diseases.

The observed neurological manifestations also coincide with those described by Zhou et al. (11), who

documented progressive neurological deterioration and subsequent leukoencephalopathy in patients with MELAS. Likewise, Latin American reports have indicated diagnostic and therapeutic difficulties related to the limited availability of resources and specialized protocols, both in Mexico and Colombia (7,12).

In this case, the fluid and electrolyte instability was likely exacerbated by multiple therapeutic interventions and the absence of a specific protocol for the prevention of respiratory distress syndrome (RDS). According to Crook et al. (10) and the recommendations of ASPEN (6), early identification of high-risk patients, the gradual initiation of nutrition, and close electrolyte monitoring are fundamental measures to reduce complications and mortality.

Unlike specialized international centers, where multidisciplinary strategies exist for the nutritional and neurological management of patients with MELAS, secondary-level hospitals continue to face structural limitations that hinder timely detection and treatment. In this regard, the case highlights the need to adapt international guidelines to the local hospital context and establish specific protocols for the prevention of retinopathy of prematurity (ROP) in pediatric patients with rare metabolic disorders.

Finally, this report underscores the importance of strengthening medical training, optimizing metabolic surveillance, and ensuring continuous electrolyte monitoring in high-risk patients. Although the outcome was fatal, the experience provides useful clinical evidence to promote preventive strategies and improve the multidisciplinary approach to pediatric patients with MELAS syndrome.

CONCLUSION

This clinical case highlights the high complexity of pediatric management in patients with MELAS syndrome, especially when neurological, gastrointestinal, and metabolic disorders coexist, increasing the risk of refeeding syndrome and mortality. The unfavorable outcome observed underscores the importance of early recognition of this complication, particularly in patients with mitochondrial diseases and chronic malnutrition.

Furthermore, the case reflects the diagnostic and therapeutic limitations that still exist in general hospitals for the management of rare metabolic diseases. In accordance with international recommendations, it is essential to implement refeeding syndrome prevention protocols that include early identification of risk factors, close electrolyte monitoring, progressive nutritional support, and multidisciplinary management.

Finally, this report contributes to the national clinical evidence on MELAS in the pediatric population and highlights the need to strengthen medical training and standardize care strategies in resource-limited settings, with the aim of improving prognosis and reducing morbidity and mortality in these patients.

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